Journal of the American College of Cardiology Vol. 47, No. 11 Suppl B

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.010

Pediatric Cardiology and Adult Congenital Heart Disease

Michael J. Landzberg, MD, FACC,* Ross Ungerleider, MD, FACC†
Boston, Massachusetts; and Portland, Oregon

In the new Congenital Heart Disease and Pediatric Cardiology subsection, 186 abstracts were submitted to the Program Committee of the 55th Annual Scientific Session, with 60 accepted and presented during 8 abstract sessions. In addition, there were 17 structured sessions at ACC.06. Altogether, 50 institutions from 11 nations participated, underscoring the diversity in "celebrating the cardiology community."

These highlights will focus on four topic areas: 1) large database analyses of populations at risk; 2) pathophysiologic studies related to clinical aspects of care; 3) the two ends of the pediatric and congenital heart disease spectrum, namely fetal and adult populations; and 4) innovative therapies, including percutaneous pulmonary valve techniques as well as technology related to patent foramen ovales (PFOs).

POPULATIONS AT RISK

In a study of databases maintained in two of the largest congenital heart disease population centers—Philadelphia and Boston—investigators compared data from their regional institutions to those accrued by the Centers for Disease Control and Prevention (CDC) national database regarding obesity. This is a pediatric epidemic with numerous health implications and a condition that may pose additional cardiovascular risk to children with acquired and congenital heart disease. Because many children with congenital heart diseases are restricted from physical activity, there remain no data to fully define the scope of the potential threat of obesity within this already at-risk population. Pinto et al. (1) showed that the prevalence of obesity in congenital heart disease patients cared for in either Philadelphia or Boston is similar to that in nonaffected adolescents as captured by the national CDC database. This lack of difference is held across the spectrum of congenital heart diseases with one exception: there were fewer obese or at-risk for obesity single-ventricle patients compared to the national population ($p = 0.003$).

Thus, the outpatient pediatric congenital cardiac population appears at no less risk for obesity than the national population, giving them additional risk factors for long-term cardiovascular disability. The authors stated that careful consideration should be given to limiting physical activities in congenital heart disease patients, weighing the potential risks of exercise against those of a sedentary lifestyle.

Although it seems almost incomprehensible, at the other end of the age spectrum, until recently there have been only general estimates of the number of adults with congenital heart diseases in the U.S. or throughout the world. These estimates were not based on much supportive data. Mackie et al. (2) analyzed a provincial database regarding physicians' claims from the province of Quebec and delineated everyone over 18 years of age who had at least one diagnostic code of a congenital heart disease lesion; patients were classified as "severe" if they had a univentricular heart, tetralogy of Fallot, an atrioventricular canal defect, truncus arterious, or transposition of the great arteries.

The investigators analyzed the database and determined, based on all health-related claims, congenital heart disease prevalence as 5.78 per 1,000, yielding a total of 22,096 adults in that region identified as having congenital heart disease. If these numbers are extrapolated to the U.S. population, for the first time, there is substantiation that there are perhaps some 800,000 adults in this country with congenital heart disease. For the first time, as well, it becomes clearly recognized that the number of adults with congenital heart disease may truly equal the pediatric population with congenital heart disease.

Additionally, some 8% of adults with congenital heart disease were classified as having severe lesions. This small percentage of patients comprised a highly morbid population utilizing a high amount of resources (Table 1). These data suggest that the medical community will need to plan for appropriate resource allocations to serve this growing population.

PATHOPHYSIOLOGY

In a small pathophysiology study from Japan, Hata (3) noted that simple lesions, such as atrial septal defects (ASDs) and ventricular septal defects (VSDs), that arise from volume and/or pressure overload in the right heart can result in sympathovagal imbalance that may be reflected in heart rate variance. This author measured the correlation between heart rate variance and respiratory frequency characteristics as well as left-to-right shunt ratio (Q_P/Q_S), both indices of sympathetic nerve activity, using Doppler echocardiography. They found a positive correlation between Q_P/Q_S and the ratio of low- to high-frequency power in ASD but not VSD patients. Conversely, Q_P/Q_S correlated

From the *Department of Cardiology, Children's Hospital, Boston Massachusetts; and the †Division of Cardiothoracic Surgery, Oregon Health and Science University, Portland, Oregon.

JACC Vol. 47, No. 11 Suppl D
June 6, 2006:D33–D6

Abbreviations and Acronyms

2D = two-dimensional
ASD = atrial septal defect
CDC = Centers for Disease Control and Prevention
CHF = congestive heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
LVV = left ventricular volume
PFO = patent foramen ovale
PVRi = pulmonary vascular resistance, indexed
RT3DE = real-time three-dimensional echocardiography
RVH = right ventricular hypertrophy
Sp_{O_2} = oxygen saturation
VSD = ventricular septal defect

negatively with the ratio of total to respiratory frequency power in ASD patients but positively in VSD patients.

The researchers concluded that untreated ASD and VSD physiologies demonstrated different effects of respiratory vagal activity on heart rate variability. This recapitulated the emerging paradigm that in congenital heart disease patients with even simple lesions, sympathetic nerve activity may be activated and suggests that potential markers may eventually be used to help predict when patients with these simple lesions should undergo surgery.

Coagulation factor abnormalities, which are thought to predispose patients to increased embolic risk after Fontan procedure, may actually precede surgical palliation. Cheung and Cheung (4) compared these factors in patients with single-ventricle congenital heart disease before the Fontan procedure with age-matched post-Fontan patients and control subjects, measuring liver function, coagulation factor levels, and pulse oximetry readings. Liver function was normal in patients before and after surgery except for mildly elevated bilirubin in the post-Fontan patients ($p = 0.027$). Compared with controls, pre-Fontan patients had lower levels of protein C, protein S, antithrombin III, and factors II, V, VII, and X, as well as having higher prothrombin times (all $p < 0.05$). Similarly, when compared to post-Fontan patients, pre-Fontan patients had lower levels of protein S ($p < 0.001$), protein C ($p = 0.06$), and antithrombin III ($p = 0.001$). Systemic oxygen saturation correlated positively with the levels of anticoagulants and procoagulants (all $p < 0.05$). Because these abnormalities coincided with the depth of systemic hypoxemia and tended to normalize after the procedure, they sway toward consideration of early intervention in such patients.

Table 1. Health Care Resource Utilization by Severe Adult Congenital Heart Disease Patients

	Relative Risk	95% Confidence Interval
Outpatient specialty care	1.25	1.19–1.32
Emergency department utilization	1.10	1.03–1.17
Hospitalization	1.31	1.20–1.44
Days in intensive care	2.06	1.74–2.44

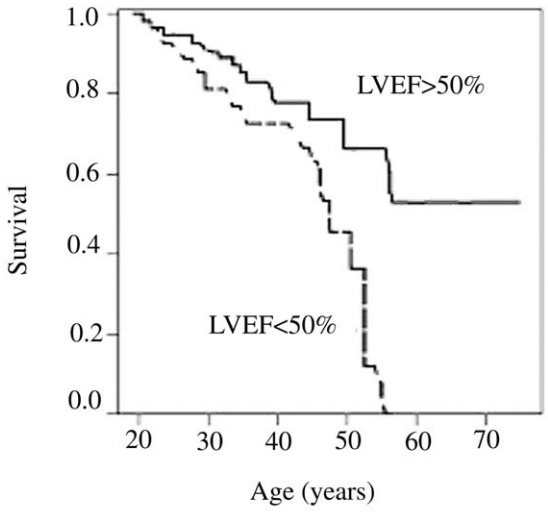

Figure 1. Impact of left ventricular dysfunction on survival in Eisenmenger syndrome. In a study of 122 patients, left ventricular dysfunction was a strong predictor of mortality. Patients with a left ventricular ejection fraction (LVEF) <50% demonstrated a sharply shortened survival curve compared to Eisenmenger patients with LVEF ≥ 50%. Reprinted with permission (5).

EVOLUTION OF EISENMENGER SYNDROME

The central defects of Eisenmenger syndrome lead to an increase in left-to-right shunting and a change in pulmonary artery pressure and resistance that produce inflammatory changes and ultimately a reversal of shunting and cyanosis. Clinicians now recognize that over the past six decades we have had no impact on the survival of this population.

Two different groups examined the markers of survival in this population, in whom risk factors such as right ventricular hypertrophy (RVH) and presence of complex anatomy are high-risk features. A Toronto group considered the impact of left ventricular dysfunction on survival among Eisenmenger patients, using medical records and echocardiograms of adult patients. In 122 patients, 75 had simple defects including ASD and VSD; median survival was 53.8 years and there were 47 deaths among the cohort of patients whose records were in the Toronto Adult Congenital Cardiac Center (5). On univariate analysis, researchers found that predictors of death included clinical signs of congestive heart failure (CHF), RVH, and left ventricular ejection fraction (LVEF) <50%. Clinical CHF (hazard ratio [HR] 2.26) and LV dysfunction (HR 3.73) remained strong predictors of mortality; patients with an LVEF <50% had a truncated survival curve compared to those with higher ejection fractions (Fig. 1).

Similarly, investigators in the United Kingdom sought to determine predictors of death in adult patients with Eisenmenger syndrome via a case-control study of 182 Eisenmenger patients from their center (6). During the study

Table 2. Predictors of Mortality in Eisenmenger Patients

Factor	Relative Risk	p Value
New York Heart Association functional class	3.0	<0.05
Signs of heart failure	10.3	<0.01
History of documented arrhythmia	12.4	<0.05
Low albumin	0.9	<0.05
High gGT	1.06	<0.05
Low potassium	0.1	<0.05

period (2001 to 2005), 18 patients died; underlying cardiac anatomy was nonrestrictive VSD (5 patients), ASD (4 patients), common arterial trunk (4 patients), transposition of great arteries with VSD (3 patients), and patent arterial duct (2 patients). A number of factors were predictive of mortality (Table 2), although neither medication nor semiquantitative echocardiographic assessment of right and left ventricular size and function predicted death. On electrocardiogram, longer QRS duration and QTc interval were associated with worse outcome (both $p < 0.05$). The authors concluded that mortality in Eisenmenger patients can be predicted with clinical and laboratory parameters and some of these markers are associated with sudden cardiac death. Taken together, these two studies emphasize that it was right-heart function, left-heart function, and arrhythmia that contributed most to death.

THE BREATHE-5 TRIAL

Bosentan (Tracleer), a dual endothelin receptor antagonist, has been shown to be effective in pulmonary arterial hypertension, and in the first-ever randomized controlled trial in the Eisenmenger population, it was studied to determine if it would have an effect on oxygen saturation (primary objective; evaluated for non-inferiority) and hemodynamics (superiority); secondary end points were exercise capacity, safety, and tolerability.

Fifty-four patients were randomized 2:1 to bosentan ($n = 37$) or placebo ($n = 17$); baseline characteristics, including mean oxygen saturation (Spo_2); mean pulmonary vascular resistance, indexed (PVRi); and 6-min walk distance, were similar between groups (7). After four months, the treatment effect on Spo_2 was 1%. Bosentan did not worsen Spo_2, proving noninferiority for the first primary end point. Efficacy analysis showed reductions in PVRi ($p = 0.04$) (the second primary end point) and mean pulmonary arterial pressure ($p = 0.04$), plus an increase in exercise capacity, as measured by 6-min walk distance ($p = 0.008$) during this relatively short four-month trial. The safety profile was comparable to that observed in previous pulmonary arterial pressure trials. The reduction of PVRi with bosentan refutes the accepted view that pulmonary resistance in the Eisenmenger population is fixed and not amenable to any other treatment.

FETAL INTERVENTION

Newer technologies are leading to more accurate measurement of fetal volumes and other parameters with tremendous implications for the growing field of fetal intervention. Using dynamic ungated four-dimensional echocardiography, Hui et al. (8) obtained measurable images from 27 (of 30) consecutive normal pregnancies, which allowed the development of normal values for right ventricular and left ventricular volumes from the 24th week of pregnancy through term.

Among various parameters, left ventricular volume (LVV) as calculated using two-dimensional (2D) echocardiography has been used to select fetuses with severe aortic stenosis for in utero intervention. Soriano et al. (9) used real-time three-dimensional echocardiography (RT3DE) to measure left ventricular diastolic volumes, and found that the median LVV by RT3DE was 2.5 ml and by 2D echocardiography was 2.8 ml, which were not significantly different. It was expected by mathematical modeling that the RT3DE volumes would tend to be smaller than those measured by 2D echocardiography, due to the more spherical nature of the left ventricle in severe fetal aortic stenosis, but this did not appear to be the case.

INNOVATIVE THERAPIES

Currently, for pulmonary insufficiency, only one valve (Bonhoeffer-Medtronic, Minneapolis, Minnesota) has been tested and evaluated in humans. The initial animal experience using a percutaneous heart valve was reported by Garay et al. (10), who implanted the Cribier-Edwards Aortic Bioprosthesis (Edwards Lifesciences, Irvine, California) pulmonary heart valve in various animals. Delivery was accomplished via both femoral and jugular vein access in acute and chronic disease models. Although size and remaining function of some of the native valves proved too difficult for the implanted valves to overcome in some cases, the researchers found the results encouraging. They plan to complete the long-term animal studies, optimize the delivery systems, and perform pulmonary replacement in clinical cases.

A novel PFO closure technique utilizing radiofrequency energy rather than an implant was attempted in 29 pigs, 7 of which had native PFOs (11). The septum was crossed at the superior rim of the fossa ovalis in 22. Radiofrequency ablation was successfully applied in all cases, and six of the seven native PFOs were closed. In the first 17 animals, 2 developed first degree block, leading to a change in electrode shape and procedural improvements that eliminated the problem in the remaining animals. At six weeks, all animals had healing fibrosis and inflammation with complete endothelialization of both right and left atrial surfaces without thrombus. The unique approach was feasible and safe in pigs and may allow for PFO closure without many of the thrombotic, arrhythmic, or erosion complications seen with device implants.

Reprint requests and correspondence: Dr. Michael J. Landzberg, Department of Cardiology, Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115-5724. E-mail: Mike.Landzberg@cardio.chboston.org.

REFERENCES

1. Pinto NM, Marino BS, Wernovsky G, et al. Obesity is prevalent, and is a significant additional comorbidity in children with congenital and acquired heart disease (abstr). J Am Coll Cardiol 2006;47 Suppl A:246A.
2. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health-care resource utilization in adults with congenital heart disease: a population-based study (abstr). J Am Coll Cardiol 2006;47 Suppl A:245A.
3. Hata T. Comparison of autonomic control between atrial septal defect and ventricular septal defect based on heart rate variability and respiration (abstr). J Am Coll Cardiol 2006:47 Suppl A:245A.
4. Cheung EWY, Cheung Y. Systemic oxygen saturation and coagulation factor abnormalities before and after the Fontan procedure. J Am Coll Cardiol 2006;47 Suppl A:244A.
5. Salehian O, Schwerzmann M, Rambihar S, et al. Left ventricular dysfunction and mortality in patients with Eisenmenger syndrome (abstr). J Am Coll Cardiol 2006;47 Suppl A:249A.
6. Diller G-P, Dimopoulos K, Kaya MG, et al. Predictors of mortality in adult patients with Eisenmenger physiology (abstr). J Am Coll Cardiol 2006;47 Suppl A:250A.
7. Landzberg M, Beghetti M, Gatzoulis MA. Bosentan improves hemodynamics and exercise capacity in Eisenmenger physiology (abstr). J Am Coll Cardiol 2006;47 Suppl A:246A.
8. Hui L, Sahn CS, Nieman PS, Wyatt S, Sahn DJ. Assessment of fetal ventricular volume by dynamic 3D/4D echocardiography in normal fetuses (abstr). J Am Coll Cardiol 2006;47 Suppl A:243A.
9. Soriano B, Tworetzky W, Marshall A, et al. Real-time 3-dimensional echocardiography for the calculation of left ventricular volumes in fetuses with aortic stenosis being considered for in-utero intervention: an in-vivo, and in-vitro validation study (abstr). J Am Coll Cardiol 2006;47 Suppl A:249A.
10. Garay F, Cao Q-L, Olin J, et al. Cribier-Edwards aortic bioprosthesis in the pulmonic position; initial animal experience (abstr). J Am Coll Cardiol 2006;47 Suppl A:239A.
11. Moore P, Feldman T, Mead H, et al. Novel non-implant radiofrequency energy catheter closure of patent foramen ovale in swine (abstr). J Am Coll Cardiol 2006;47 Suppl A:249A.